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GUADCO INC

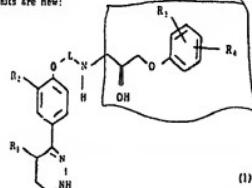
01.09.97 US-02179 (+US-392232) (13.02.91) A61k-31/50

CD6-227-04

New pyridazine derivs. - have beta blocking activity for treatment of congestive heart failure.

C61-019437 RIAT BE CM DE CK ES FR GB GR IT LU NL SEI

Pyridazine derivs. of formula (I) and their acid addin salts are new:



07-D10, 12-E2, 12-F4B, 12-F1B

 $R_1 = H$ or lower alkyl; $R_2 = H$, halo, C_F , CN, lower alkyl or lower alkoxy;L = O, $(R_3R_4)_nCONH(R_5)CH_2$ or $C_6H_{10}N_1$; (grp. (a)) or $(C_6H_5)_2N$; (grp. (b)); $R_3 = R_4 = H$ or lower alkyl;

n = 1-3;

p = 2-6;

 $R_1, R_2 = H$, alkoxy, morpholine, CN, halo, C_F , alkyl, alkylsulphonyl, alkoxyalkyl, cycloalkylalkoxyalkyl, NO_2 , OH, alkenyloxy, NH₂ or mono- or di-alkylamino.**MORE SPECIFICALLY** $R_1 = H$ or Me; $R_2 = H$ or Cl;

L = (a);

n = 1 or 3;

 $R_3 = R_4 = H$; $R_3R_4 = H$ or Me; $R_1 = H$; $R_2 = CN, Cl$ or Me .

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USE(I) are useful for treating congestive heart failure. In tests (I) exhibit inotropic and β -adrenergic blocking activity. Dose is 0.1-5 mg/kg 1-4 times a day.**SPECIFICALLY CLAIMED**

1. Compounds of formula (I)
6-(4-(N-(2-(1-cyanoethoxy)-1-hydroxypropyl)amino)-2-methylpropyl)succinimidoxy-5-chlorophenyl)-4,5-dihydro-2(H)-pyridazinones; and
6-(4-(N-(2-(1-(2-cyanoethoxy)-(2S)-1-hydroxypropyl)amino)ethylcarbamoyloxypropoxy-3-chlorophenyl)-4,5-dihydro-2(H)-pyridazinone.

WIDER DISCLOSURE

Intermediates of formula (VII) (see 'Starting Materials') and (VIII) (see 'Preparation') are new.

PREPARATION

(I)

 R_1 R_2 R_3 R_4 R_5 R_6 R_7 R_8 R_9 R_{10} R_{11} R_{12} R_{13} R_{14} R_{15} R_{16} R_{17} R_{18} R_{19} R_{20} R_{21} R_{22} R_{23} R_{24} R_{25} R_{26} R_{27} R_{28} R_{29} R_{30} R_{31} R_{32} R_{33} R_{34} R_{35} R_{36} R_{37} R_{38} R_{39} R_{40} R_{41} R_{42} R_{43} R_{44} R_{45} R_{46} R_{47} R_{48} R_{49} R_{50} R_{51} R_{52} R_{53} R_{54} R_{55} R_{56} R_{57} R_{58} R_{59} R_{60} R_{61} R_{62} R_{63} R_{64} R_{65} R_{66} R_{67} R_{68} R_{69} R_{70} R_{71} R_{72} R_{73} R_{74} R_{75} R_{76} R_{77} R_{78} R_{79} R_{80} R_{81} R_{82} R_{83} R_{84} R_{85} R_{86} R_{87} R_{88} R_{89} R_{90} R_{91} R_{92} R_{93} R_{94} R_{95} R_{96} R_{97} R_{98} R_{99} R_{100} R_{101} R_{102} R_{103} R_{104} R_{105} R_{106} R_{107} R_{108} R_{109} R_{110} R_{111} R_{112} R_{113} R_{114} R_{115} R_{116} R_{117} R_{118} R_{119} R_{120} R_{121} R_{122} R_{123} R_{124} R_{125} R_{126} R_{127} R_{128} R_{129} R_{130} R_{131} R_{132} R_{133} R_{134} R_{135} R_{136} R_{137} R_{138} R_{139} R_{140} R_{141} R_{142} R_{143} R_{144} R_{145} R_{146} R_{147} R_{148} R_{149} R_{150} R_{151} R_{152} R_{153} R_{154} R_{155} R_{156} R_{157} R_{158} R_{159} R_{160} R_{161} R_{162} R_{163} R_{164} R_{165} R_{166} R_{167} R_{168} R_{169} R_{170} R_{171} R_{172} R_{173} R_{174} R_{175} R_{176} R_{177} R_{178} R_{179} R_{180} R_{181} R_{182} R_{183} R_{184} R_{185} R_{186} R_{187} R_{188} R_{189} R_{190} R_{191} R_{192} R_{193} R_{194} R_{195} R_{196} R_{197} R_{198} R_{199} R_{200} R_{201} R_{202} R_{203} R_{204} R_{205} R_{206} R_{207} R_{208} R_{209} R_{210} R_{211} R_{212} R_{213} R_{214} R_{215} R_{216} R_{217} R_{218} R_{219} R_{220} R_{221} R_{222} R_{223} R_{224} R_{225} R_{226} R_{227} R_{228} R_{229} R_{230} R_{231} R_{232} R_{233} R_{234} R_{235} R_{236} R_{237} R_{238} R_{239} R_{240} R_{241} R_{242} R_{243} R_{244} R_{245} R_{246} R_{247} R_{248} R_{249} R_{250} R_{251} R_{252} R_{253} R_{254} R_{255} R_{256} R_{257} R_{258} R_{259} R_{260} R_{261} R_{262} R_{263} R_{264} R_{265} R_{266} R_{267} R_{268} R_{269} R_{270} R_{271} R_{272} R_{273}

$R_{11} = H$;
 $R_{11} =$ amino protecting gp.;
or $R_{11} + R_{11} =$ divalent amino protecting gp.

EXAMPLE

A solution of 499 mg 6-(4-(2-aminophenylcarbamoyl)-methoxy)phenyl-5-methyl-4,5-dihydro-1(1H)-pyridazinone and 393 mg (25) (+)-3-phenoxy-1,2-epoxyp propane in 10 ml MeCN is refluxed for 10 hr. then evapd. The residue is taken up in CHCl₃/MeOH (1:1) (10ml) then flash chromatographed on gel eluting with CHCl₃/MeOH (10:1) (100 ml) then CHCl₃/MeOH/NH₃/OH (90:10:2) (1 l) to give 423 mg (60%) 6-(4-(N-(2-(3-phenoxy-2-hydroxypropyl)anilolethyl)carbamoylmethoxyphenyl)-5-methyl-4,5-dihydro-1(1H)-pyridazinone (1a).

This is dissolved in 15 ml EtOAc. 5 ml ether are added. 12 ml 0.1 N Maleic acid in ether are added with stirring. The ppt. is filtered, washed with ether and dried overnight at 50°C in vacuo to give (1a) maleate, m.p. 58-73°C (53pp985EDwgt0/0).

(E) ISR: No Search Report.

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